

Association of Blood Inflammatory Biomarkers with Clinical Outcomes in Patients with AECOPD: An 8-Year Retrospective Study in Beijing

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Purpose: To discover potential inflammatory biomarkers, which can compare favorably with traditional biomarkers, and their best cut-offs at first admission to predict clinical outcomes (short-term and long-term) and the risk of readmission among acute exacerbations of chronic obstructive pulmonary disease (AECOPD) patients.

Patients and Methods: Novel inflammatory biomarkers (such as the neutrophil–lymphocyte ratio [NLR], platelet–lymphocyte ratio [PLR], etc.) were compared with traditional biomarkers by Pearson's correlation test. Logistic regression analysis and receiver operating characteristic (ROC) curves were applied to judge the accuracy of these novel biomarkers to predict in-hospital mortality.

Results: Surviving AECOPD patients had lower NLR, PLR, and lymphocyte-to-monocyte ratios than non-survival patients (all $P < 0.001$). According to Pearson's correlation test, there was a linear correlation between novel and traditional biomarkers (all $P < 0.05$). In terms of a single biomarker, the AUC value of NLR was the largest, which was not inferior to C-reactive protein ($Z-P = 0.064$), and superior to erythrocyte sedimentation rate ($Z-P = 0.002$) and other novel single inflammatory biomarkers (all $Z-P < 0.05$). The mortality of patients with $NLR \geq 4.43$ was 2.308-fold higher than that of patients with $NLR < 4.43$. After dividing patients into a higher or lower NLR group, pooled results showed that patients with $NLR \geq 4.43$ had a higher rate of treatment failure, intensive care unit admission, longer hospital length of stay, one-year mortality after the index hospitalization, and overall mortality than patients with $NLR < 4.43$ (all $P < 0.001$). Patients with $NLR \geq 4.43$ were associated with higher and earlier first readmission due to AECOPD than patients with lower NLR.

Conclusion: NLR was the best to forecast the clinical prognosis and readmission risk among AECOPD patients, which was not inferior to CRP, and the best cut-off value of NLR was 4.43.

Keywords: acute exacerbations of chronic obstructive pulmonary disease, neutrophil–lymphocyte ratio, mortality, inflammatory biomarkers, readmission rate, treatment failure rate

Background

Chronic obstructive pulmonary disease (COPD), characterized by persistent respiratory symptoms and airflow limitation,¹ is an important public health threat with high mortality worldwide. In 2019, COPD accounted for 212.3 million prevalent cases and 3.3 million deaths globally.² The World Health Organization (WHO) estimated that COPD will rise to the third leading cause of death in 2030, with the corresponding economic burden ranking fifth.³ COPD-caused mortality is largely related to acute exacerbation of COPD (AECOPD), which is defined as an acute worsening of respiratory symptoms in COPD (increased dyspnea, increased sputum purulence or volume together with worse cough or wheezing) and requiring additional therapy.¹ According to previous studies, the short-term mortality of AECOPD patients in China ranged from 8.4%⁴ to 12.2%,⁵ and the mortality increased with the number of readmissions

for AECOPD.⁶ Based on a post hoc analysis that included 120 patients, the overall mortality was 26 (37.7%), with 3.4 mean duration of follow-up.⁷ As a result, in order to provide more appropriate treatment and management of AECOPD patients, it is essential to find appropriate biomarkers that can be used for early and precise identification of patients' short-term and long-term clinical prognosis and readmission risk.

Since the most common causes of AE are respiratory tract infections, the most frequently used forecast biomarkers in clinical work among AECOPD patients are C-reactive protein (CRP), procalcitonin (PCT) and erythrocyte sedimentation rate (ESR), with the support of previous studies and the experience of clinicians. According to previous studies, higher CRP was associated with higher noninvasive positive pressure ventilation (NIPPV) failure during hospitalization and readmission rates among patients with AECOPD.^{8,9} PCT and ESR can distinguish AECOPD patients from AECOPD patients with infection (such as community acquired pneumonia [CAP]).¹⁰ Among them, PCT had guiding value for the selection of ventilation switching points in sequential mechanical ventilation, predicting bacterial infection and the use of antibiotic prescriptions.^{5,11–14} Due to the lack of relevant laboratory inspection equipment and the relatively high cost, the application of traditional inflammatory biomarkers, such as PCT and ESR, was limited at some grass root levels of rural medical and health institutions in China. This pushed us to find more accessible and cost-effective biomarkers to predict the short- and long-term clinical outcomes for these patients. Recently, the ratio of some inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), has drawn great attention from physicians, since they can be assessed using a simple complete blood count (CBC) test.^{5,10,15–19} Several studies have shown that the value of NLR might be the best biomarker to predict the prognosis of AECOPD patients,^{19,20} while other studies have reported that blood indicators such as PLR are the best.^{21,22} However, most of the studies just focused on limited kinds of inflammatory biomarkers and there is a paucity of studies to comprehensively confirm the best inflammatory biomarkers versus other traditional or novel inflammatory biomarkers. At the same time, direct comparisons between different areas under the curve (AUCs) were not confirmed by statistical methods. Moreover, due to the limited number of patients and different study designs in those studies, the cut-off values of NLR (ranging from 3.18²³ to 16.83²⁴) or other blood inflammatory biomarkers were inaccurate and inconsistent.²⁵

Therefore, we performed the largest sample size clinical study to date to explore the best single or combined inflammatory biomarkers to predict the clinical prognosis of AECOPD patients and evaluate their best cut-off values. In this study, we proposed that the NLR is superior to other novel inflammatory biomarkers refined from the CBC test and was not inferior to traditional inflammatory biomarkers like CRP and ESR in predicting the short- and long-term clinical outcomes among AECOPD patients. We hope to provide more rigorous and sufficient evidence-based medical evidence for clinicians to quickly judge the prognosis of patients and guide further treatment.

Materials and Methods

Data Source and Population

This was a single-center, retrospective study that included patients with AECOPD who were admitted to Beijing Chao-Yang Hospital from April 4th, 2013, to June 30th, 2021. All patient data were collected from the Hospital electronic medical record database (EMRD), which was operated by Beijing Chao-Yang Hospital, and the quality of the data was assured.²⁶ The hospitalization records for patients aged ≥ 40 years old with a primary discharge diagnosis of AECOPD (ICD-10 codes J44.0–J44.9) were included in this study and were checked by two authors independently (SS and ZJZ). The diagnosis of COPD and AECOPD in Chao-Yang Hospital followed the global initiative for chronic obstructive lung disease (GOLD) guidelines over the years (detailed diagnostic criteria are listed in [Supplementary Material 1](#)). Hospitalized patients with corona virus disease 2019 (COVID-19) were not included during this study period, because the policy of Beijing Chao-Yang Hospital. Eventually, patients without CBC data or patients who did not undergo CBC testing within 48 hours after admission were excluded from this study. The clinical features and examination results in multiple hospitalizations of one patient could be correlated with each other. Thus, if one patient had several AECOPD hospitalization records, the first one was regarded as the index hospitalization and the subsequent records were considered as outcomes. This study was approved by the Research Ethics Board of Beijing Chao-Yang Hospital (project approval number: 2020-ke-544) and complied with the Declaration of Helsinki. All data extracted from the database were

deidentified prior to analysis, making it impossible to identify individual-level data either in this study or in the retrieved database. Informed consent was waived due to the anonymous and mandatory nature of the data.

Data Collection and Quality Control

The data obtained in this study included patients' demographic characteristics (age and sex, etc.), current smoking status, comorbidities, clinical symptoms, physical signs, laboratory tests of blood (CBC, arterial blood gas analysis, and blood chemistry, etc.), inflammatory markers (NLR, PLR, lymphocyte-to-monocyte ratio [LMR], platelet-to-mean platelet volume ratio [PMR], eosinophil-to-neutrophil ratio [ENR], eosinophil-to-lymphocyte ratio [ELR], CRP, PCT). Regarding the clinical outcomes, we included participant pharmacotherapy for AECOPD, respiratory support therapy (noninvasive mechanical ventilation [NIMV], invasive mechanical ventilation [IMV] or NIMV combined with IMV), length of stay (LOS), LOS > 14 days, admission to the intensive care unit (ICU), cost, first readmission due to AECOPD within 1 month/2 months/3 months/12 months/15 months/24 months after discharge (readmission data were obtained from Beijing Public Health Information Centre), organ failure, respiratory failure, treatment failure, in-hospital mortality (during the index hospitalization period), one-year mortality after the index hospitalization, and overall mortality (the number of deaths during the last hospitalization based on the records from the Beijing Chao-Yang Hospital EMRD was divided by total cases). Spirometry was performed during the index hospitalization period among a limited population. The results of spirometry in other hospitals could not be found in the Hospital EMRD of Beijing Chao-Yang Hospital. Microbiological data of patients could not be obtained due to the lack of electronically available microbiological data.

Definitions

Organ failure was defined as either one of the following events: a) respiratory failure; b) liver failure; c) renal failure; or d) heart failure.

Treatment failure was defined as either one of the following events: a) IMV received during admission; b) admission to the ICU; c) organ failure; d) LOS > 14 days; or e) death during hospitalization.

Statistical Analysis

For continuous variables with a normal distribution, the mean $\pm$ standard deviation was employed to describe the presentation of data. The median and interquartile range (IQR) were employed for nonparametric continuous variables. Categorical variables are summarized using counts and percentages. Continuous variables were compared between two groups with *t* tests if the data were normally distributed; otherwise, the Mann–Whitney *U*-test was employed. Categorical variables were judged by using the chi-square test or Fisher's exact test when the sample size was small. Spearman correlation analysis was used for correlation analysis, and the results were reported as correlation coefficients with corresponding *P* values. Receiver-operating characteristic (ROC) curves were applied to evaluate the ability of inflammatory biomarkers to predict in-hospital mortality. Because of the lack of established threshold values of inflammatory biomarkers, the best cut-off values were calculated in this study by using Youden's index. The inflammation biomarkers with the largest area under the ROC curve were chosen to classify AECOPD patients to judge the clinical application value of the inflammation biomarkers. The *Z* test was used to compare the AUC value between each two indicators.²⁷ Finally, to determine whether any of the clinical signs, symptoms, or laboratory test data were independently associated with in-hospital mortality, we performed logistic regression analyses by using a conditional forward stepwise regression model, and the results were reported as adjusted odds ratios (ORs), 95% confidence intervals (CIs) and *P* values. In addition, to make the results of this research feasible to clinicians, a nomogram was established by the "rms" package in R software (version 3.6.0). A calibration curve was plotted to verify the relationship between the event rate predicted by the nomogram model and the actual situation. The bootstrap self-sampling method (the number of self-sampling times *B*=1000) was used for internal validation to reduce over-fitting deviation, and the concordance index (C-index) and ROC curve were used to evaluate the prediction accuracy of the nomogram. An AUC or C-Index less than 0.65 indicates poor model discrimination, 0.65 to 0.75 indicates that the model has some discriminatory ability, and a value greater than 0.75 indicates that the model has a good discriminatory ability.²⁸ Finally, a Kaplan–Meier (K–M) curve was applied to visualize the data of the first readmission due to AECOPD after discharge among AECOPD patients who were included

in this study. All values of p less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY) software, R software (version 3.6.0) and MedMalc software.

Result

Figure 1 shows the selection process of patients. There were 7059 hospitalization records for patients aged ≥ 40 years old with a primary discharge diagnosis of AECOPD (ICD-10 codes J44.0–J44.9) from April 4th, 2013 to June 30th, 2021. We deleted 2409 records of repeated admissions and retained 4650 initial admission records. A total of 265 patients without CBC data and 2 patients with abnormal data were excluded. In addition, 148 patients whose first CBC exceeded 48 h after admission were excluded from this study. Finally, 4235 eligible patients were included in this study. Among these patients, 64 cases were classified into the non-survival group, and 4171 cases were classified into the survival group. Four hundred and forty-nine patients had spirometry during the index hospitalization, the median forced expiratory volume in one second (FEV1) was 1.18 L (0.77–1.81 L), and the median FEV1/forced vital capacity was 48.15% (38.40–59.83%). Due to the limited cases reported for spirometry, they were not included in further analyses.

Baseline Characteristics of the Included Subjects

General characteristics are listed in Table 1. The median age of all patients was 71.00 (63.00–78.00) years, and the median body mass index (BMI) was 22.96 (20.07–26.02) kg/m². Among all of these AECOPD patients, 74.1% were male, 23.7% were current smokers, and 49.9% were former smokers. Regarding comorbidities, cardiovascular disease was the most common disease (69.7%), followed by hypertension (45.2%) and diabetes mellitus (16.3%). Comparing the parameters of the non-survival and survival groups at admission, there were no significant differences between them for sex ($p = 0.205$), BMI ($p = 0.435$) or smoking history ($p = 0.468$). However, the pooled results showed that patients were older in the non-survival group than in the survival group (79.00 [74.25–85.75] vs 71.00 [63.00–78.00], $P < 0.001$). In terms of symptoms, the survival group was more likely to have breathe hard than the non-survival group (817 [19.6%] vs 5 [7.8%], $P = 0.018$). In addition, the total number of comorbidities in the non-survival group was significantly higher than that in the survival group (3.00 [2.00–4.00] vs 2.00 [0.00–3.00], $P < 0.001$). More details can be found in Table 1.

Laboratory Tests, Treatments and Clinical Outcomes

Compared with the survival group, the non-survival group had a significantly elevated leukocyte count (8.91 [6.71–12.61] vs 6.76 [5.44–8.67], $P < 0.001$), neutrophil count (7.96 [5.02–11.39] vs 4.49 [3.32–6.31], $P < 0.001$), red blood cell distribution width (RDW) (14.40 [13.73–15.90] vs 13.20 [12.60–14.00], $P < 0.001$) and mean platelet volume (MPV) (10.70 [9.60–11.60] vs 10.20 [9.70–10.90], $P = 0.043$). However, the non-survival group showed markedly lower lymphocyte counts (0.75 [0.51–1.12] vs 1.40 [0.99–1.88], $P < 0.001$), eosinophil counts (0.02 [0.00–0.11] vs 0.11 [0.03–0.22]), platelet counts (179.00

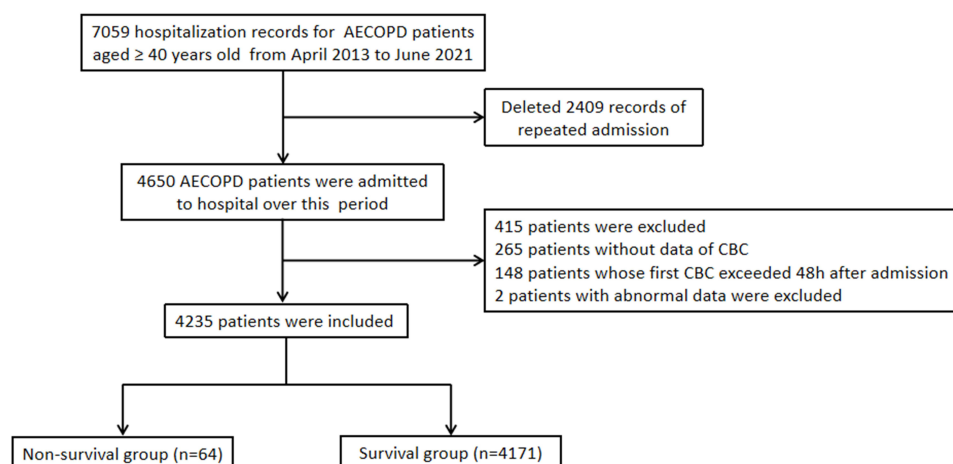


Figure 1 Patient flow chart.

Table I Baseline Characteristics of Patients

Characteristics	Overall (n=4235)	Survivor (n=4171)	Non-Survivor (n=64)	P-value
Demographics				
Male (n, %)	3137(74.1%)	3094(74.2%)	43(67.2%)	0.205
Age, year (median, 25th–75th percentiles)	71.00(63.00–78.00)	71.00(63.00–78.00)	79.00(74.25–85.75)	<0.001
BMI, kg/m ² (median, 25th–75th percentiles) (n=1513)	22.96(20.07–26.02)	22.96(20.10–26.02)	23.15(19.39–24.22)	0.435
Smoking status (n, %)(n=4125)				
Ever smoker	3037(73.6%)	2996(73.7%)	41(69.5%)	0.468
Current smoker	977(23.7%)	967(23.8%)	10(16.9%)	0.220
Former smoker	2060(49.9%)	2029(49.9%)	31(52.5%)	0.687
Never smoker	1088(26.4%)	1070(26.3%)	18(30.5%)	0.468
Pack year (median, 25th–75th percentiles) (n=2864)	365.00(273.75–547.50)	365.00(273.75–547.50)	365.00(182.50–365.00)	0.010
Symptom (n, %)				
Chest distress	351(8.3%)	346(8.3%)	5(7.8%)	0.889
Breathe hard	822(19.4%)	817(19.6%)	5(7.8%)	0.018
Cough	3355(79.2%)	3308(79.3%)	47(73.4%)	0.251
Expectoration	2912(68.8%)	2871(68.8%)	41(64.1%)	0.414
Comorbidities (n, %)				
Diabetes mellitus	681(16.3%)	663(15.9%)	18(28.1%)	0.08
Chronic renal failure	261(6.3%)	194(4.7%)	22(34.4%)	<0.001
Heart failure	136(3.3%)	126(3.0%)	10(15.6%)	<0.001
Cardiovascular disease	2906(69.7%)	2849(68.3%)	57(89.1%)	<0.001
Arrhythmia	458(11.0%)	443(10.6%)	15(23.4%)	0.001
Hypertension	1884(45.2%)	1845(44.2%)	39(60.9%)	0.008
Cerebrovascular disease	529(12.7%)	511(12.3%)	18(28.1%)	<0.001
Malignancy	209(5.0%)	198(4.7%)	11(17.2%)	<0.001
Anxiety/depression	110(2.6%)	109(2.6%)	1(1.6%)	0.600
Osteoporosis	126(3.0%)	125(3.0%)	1(1.6%)	0.503
≥2 comorbidities	2365(56.7%)	2309(55.4%)	56(87.5%)	<0.001
None	1050(25.2%)	1046(25.1%)	4(6.3%)	0.001
Total number of comorbidities (median, 25th–75th percentiles)	2.00(1.00–3.00)	2.00(0.00–3.00)	3.00(2.00–4.00)	<0.001

(Continued)

Table 1 (Continued).

Characteristics	Overall (n=4235)	Survivor (n=4171)	Non-Survivor (n=64)	P-value
Spirometry (median, 25th–75th percentiles) (n=449)				
Forced expiratory volume in one second	1.18(0.77–1.81)	1.18(0.77–1.79)	133.4 ^a	0.084
Forced expiratory volume in one second/ forced vital capacity	48.15(38.40–59.83)	48.10(38.37–59.78)	103.60 ^a	0.085

Notes: ^aAmong patients who had spirometry, only one patient died during the index hospitalization.

Abbreviation: BMI, body mass index.

[134.50–241.00] vs 206.00 [164.00–255.00]) and hemoglobin levels (101.50 [80.00–128.25] vs 129.00 [107.00–143.50]) than the survival group. Regarding biochemistry values, blood glucose, blood urea nitrogen (BUN), serum creatinine, serum glutamic-oxaloacetic transaminase (SGOT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were significantly higher ($p < 0.001$) in the non-survival group versus survival group. In contrast, patients in the survival group had higher protein, albumin and low-density lipoprotein (LDL) levels ($p < 0.001$) than patients in the non-survival group. Differences in sodium, potassium, serum glutamic pyruvic transaminase (SGPT), monocyte count, mean corpuscular volume (MCV) and arterial blood gases were not significant between these two groups (Table 2).

Table 2 Laboratory Parameters, Treatment and Clinical Outcome of Patients

Characteristics	Overall (n=4235)	Survivor (n=4171)	Non-Survivor (n=64)	P-value
Arterial blood gases (median, 25th–75th percentiles)				
pH (N=1017)	7.40(7.37–7.42)	7.40(7.37–7.43)	7.38(7.33–7.40)	0.089
PaCO ₂ (mmHg) (N=992)	39.15(34.00–48.40)	39.10(34.00–48.10)	44.80(31.48–63.73)	0.464
PaO ₂ (mmHg) (N=992)	79.55(69.73–91.58)	79.50(69.80–91.40)	75.20(63.08–95.05)	0.867
HCO ₃ [−] (mmol/L) (N=991)	24.60(21.80–28.70)	24.60(21.90–28.63)	27.20(20.55–31.45)	0.684
PaO ₂ /FiO ₂ (mmHg) (N=883)	377.95(332.65–436.30)	377.90(332.70–436.05)	392.20(325.55–468.73)	0.535
Respiratory Index (N=786)	0.30(0.10–0.40)	0.30(0.20–0.40)	0.10(0.20–0.40)	0.754
Oxygen saturation (%) (N=992)	95.60(93.10–97.20)	95.60(93.10–97.20)	94.50(89.18–96.58)	0.328
Hemogram values (median, 25th–75th percentiles)				
Leukocyte count ($\times 10^9/L$)	6.77(5.45–8.73)	6.76(5.44–8.67)	8.91(6.71–12.61)	<0.001
Neutrophil count ($\times 10^9/L$)	4.53(3.33–6.39)	4.49(3.32–6.31)	7.96(5.02–11.39)	<0.001
Lymphocytes count ($\times 10^9/L$)	1.39(0.97–1.87)	1.40(0.99–1.88)	0.75(0.51–1.12)	<0.001
Monocyte count ($\times 10^9/L$)	0.47(0.34–0.61)	0.46(0.34–0.61)	0.49(0.34–0.70)	0.235
Eosinophil count ($\times 10^9/L$)	0.11(0.03–0.22)	0.11(0.03–0.22)	0.02(0.00–0.11)	<0.001
Erythrocyte count ($\times 10^9/L$)	4.34(3.95–4.73)	4.34(3.95–4.73)	3.96(3.19–4.45)	<0.001
Platelet count ($\times 10^9/L$)	205.00(163.50–255.00)	206.00(164.00–255.00)	179.00(134.50–241.00)	0.014
Hemoglobin (g/dL)	129.00(106.00–143.00)	129.00(107.00–143.50)	101.50(80.00–128.25)	<0.001
MCV (fL)	92.00(88.90–95.50)	92.00(88.90–95.50)	92.00(88.95–97.63)	0.504

(Continued)

Table 2 (Continued).

Characteristics	Overall (n=4235)	Survivor (n=4171)	Non-Survivor (n=64)	P-value
RDW (%) (N=4234)	13.20(12.70–14.00)	13.20(12.60–14.00)	14.40(13.73–15.90)	<0.001
MPV (fL) (N=4189)	10.30(9.70–10.90)	10.20(9.70–10.90)	10.70(9.60–11.60)	0.043
Biochemistry values (median, 25th–75th percentiles)				
Blood glucose (mg/dL) (N=3907)	4.84(4.27–6.00)	4.83(4.27–5.97)	6.17(4.88–7.83)	<0.001
BUN (mg/dL) (N=1943)	5.81(4.68–7.24)	5.79(4.67–7.17)	10.23(7.07–15.36)	<0.001
Serum creatinine (mg/dL) (N=4122)	68.90(57.80–82.10)	68.60(57.80–81.90)	80.20(67.10–127.0)	<0.001
Sodium (mmol/L) (N=4159)	140.40(137.70–142.50)	140.40(137.70–142.50)	141.00(137.10–144.90)	0.118
Potassium (mmol/L) (N=4158)	4.00(3.70–4.30)	4.00(3.70–4.30)	4.00(3.70–4.50)	0.245
SGOT (U/L) (N=4074)	20.00(17.00–26.00)	20.00(17.00–26.00)	28.00(20.00–44.50)	<0.001
SGPT (U/L) (N=4077)	17.00(12.00–23.00)	17.00(12.00–23.00)	17.00(11.75–29.25)	0.426
Protein (g/dL) (N=2171)	63.40(59.40–67.50)	63.50(59.50–67.50)	56.40(49.00–60.90)	<0.001
Albumin (g/dL) (N=4015)	35.80(32.30–38.80)	35.9(32.40–38.80)	28.20(24.6–31.90)	<0.001
LDL (mmol/L) (N=3897)	2.30(1.80–2.88)	2.30(1.80–2.88)	1.92(1.42–2.59)	<0.001
NT-proBNP (ng/L) (N=3132)	178.40(68.54–646.50)	174.70(68.74–610.83)	1960.00(742.85–5236.50)	<0.001
D-Dimer (mg/L) (N=1467)	0.52(0.27–1.16)	0.52(0.27–1.11)	3.41(0.76–4.68)	<0.001
D-Dimer abnormal (n, %)	768(52.4%)	748(51.9%)	20(80.0%)	0.005
Inflammatory markers (median, 25th–75th percentiles)				
NLR (N=4232)]	3.18(2.06–5.60)	3.14(2.05–5.48)	9.28(5.42–18.42)	<0.001
PLR (N=4232)	146.62(104.92–216.07)	145.63(104.37–213.78)	230.71(176.67–315.84)	<0.001
LMR (N=4232)	0.32(0.22–0.50)	0.32(0.22–0.49)	0.59(0.40–1.02)	<0.001
PMR (N=4186)	20.19(15.38–25.75)	20.19(15.43–25.78)	15.96(12.15–24.77)	0.005
CRP (mg/L) (N=3668)	0.78(0.34–2.64)	0.77(0.33–2.59)	6.28(1.44–9.94)	<0.001
ESR (mm/L) (N=3966)	10.00(3.00–23.25)	10.00(3.00–23.00)	23.50(13.00–44.00)	<0.001
ENR (N=4232)	0.03(0.01–0.05)	0.03(0.01–0.06)	0.00(0.00–0.02)	<0.001
ELR (N=4232)	0.08(0.02–0.15)	0.08(0.02–0.15)	0.03(0.00–0.13)	0.001
Treatment (n, %)				
Bronchodilator	3708(87.6%)	3659(87.7%)	49(76.6%)	0.007
Corticosteroid nebulization	2808(66.3%)	2775(66.5%)	33(51.6%)	0.012
Systemic corticosteroid therapy	903(21.3%)	883(21.2%)	20(31.3%)	0.051
Antimicrobial therapy	3687(87.1%)	3633(87.1%)	54(84.4%)	0.519
Antifungal agents	433(10.2%)	414(9.9%)	19(29.7%)	<0.001
Expectorant	3691(87.2%)	3640(87.3%)	51(79.7%)	0.072

(Continued)

Table 2 (Continued).

Characteristics	Overall (n=4235)	Survivor (n=4171)	Non-Survivor (n=64)	P-value
Respiratory support				
NIMV	354(8.4%)	336(8.1%)	18(28.1%)	<0.001
IMV	40(0.9%)	30(0.7%)	10(15.6%)	<0.001
NIMV+IMV	51(1.2%)	40(1.0%)	11(17.2%)	<0.001
Clinical outcome and the prognosis (n, %)				
Respiratory failure	1215(28.8%)	1164(28.0%)	51(79.7%)	<0.001
Organ failure	2241(52.9%)	2179(52.2%)	62(96.9%)	<0.001
LOS, days (median, 25th–75th percentiles)	10.00(8.00–14.00)	10.00(8.00–14.00)	15.00(7.00–26.25)	0.003
LOS>14 days	866(20.4%)	833(20.0%)	33(51.6%)	<0.001
Admitted to ICU	168(4.0%)	139(3.3%)	29(45.3%)	<0.001
Hospitalization expenses (median, 25th–75th percentiles) (N=4213)	13,703.46(10,008.83–19,553.79)	13,595.32(9969.10–19,154.57)	35,998.17(19,460.16–89,472.84)	<0.001

Abbreviations: pH, potential of hydrogen; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; HCO₃⁻, bicarbonate; FiO₂, fraction of inspired oxygen; MCV, mean corpuscular volume; RDW, red cell volume distribution width; MPV, Mean platelet volume; BUN, blood urea nitrogen; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PMR, platelet to mean platelet volume ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ENR, eosinophil to neutrophil ratio; ELR, eosinophil to lymphocyte ratio; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation; LOS, length of hospital stay; ICU, intensive care unit.

The inflammatory biomarkers that we were interested in were significantly different between these two groups. The non-survival group had significantly higher NLR ($p < 0.001$), PLR ($p < 0.001$), LMR ($p < 0.001$), CRP ($p < 0.001$) and ESR ($p < 0.001$) than the survival group. However, PMR ($p = 0.005$), ENR ($p < 0.001$) and ELR ($p = 0.001$) were markedly lower in the non-survival group compared with the survival group. More details are listed in [Table 2](#). We also verified the correlation between these novel and traditional inflammatory biomarkers. NLR, PLR, LMR and PMR correlated positively with CRP ($r = 0.467$, $r = 0.351$, $r = 0.437$, $r = 0.145$, $P < 0.001$), as well as ESR ($r = 0.269$, $r = 0.348$, $r = 0.243$, $r = 0.321$, $P < 0.001$). ENR and ELR correlated negatively with CRP ($r = -0.277$, $r = -0.076$, $P < 0.001$) and ESR ($r = -0.159$, $P < 0.001$; $r = -0.040$, $P = 0.011$). All the differences in correlations reached statistical significance, which indicated that these novel inflammatory biomarkers have the potential to replace traditional inflammatory biomarkers. These results are listed in [Supplementary Table 1](#).

In terms of treatment, there was no significant difference between the non-survival group and the survival group in the usage of systematic corticosteroids, antimicrobials and expectorants. Patients in the non-survival group had a significantly higher rate of using antifungal agents (19 [29.7%] vs 414 [9.9%], $P < 0.001$) and all terms of respiratory support (NIMV, IMV and NIMV+IMV) ($p < 0.001$) than those in the survival group. However, the application of bronchodilators (3659 [87.7%] vs 49 [76.6%], $P = 0.007$) and corticosteroid nebulization (2775 [66.5%] vs 33 [51.6%], $P = 0.012$) was higher in the survival group than in the non-survival group. Regarding clinical outcomes, the non-survival group had a longer LOS (10.00 [8.00–14.00] vs 15.00 [7.00–26.25], $P = 0.03$), higher risk of ICU admission (29 [45.3%] vs 139 [3.3%], $P < 0.001$) and more hospitalization expenses (13,595.32 [9969.10–19,154.57] vs 35,998.17 [19,460.16–89,472.84], $P < 0.001$) than the survival group ([Table 2](#)).

Predictive Power of NLR and Other Novel Inflammatory Biomarkers for in-Hospital Mortality

[Table 3](#) shows that the NLR had a maximum area under the AUC (0.847; 95% CI, 0.810–0.884; $P < 0.001$) compared with other single inflammatory biomarkers (with Z-P value < 0.05). The AUCs of RDW, ELR and PMR

Table 3 ROC Curve Data

	Cut-Off	Sensitivity	Specificity	AUC	P-value	95% CI	Z-P-value ^a
Single indicator							
NLR	4.43	0.891	0.659	0.847	<0.001	0.810–0.884	NE
LMR	0.38	0.813	0.609	0.773	<0.001	0.719–0.826	0.003
ENR	0.01	0.734	0.709	0.745	<0.001	0.697–0.794	<0.001
PLR	176.49	0.766	0.635	0.709	<0.001	0.643–0.775	<0.001
ELR	0.04	0.625	0.661	0.616	0.010	0.540–0.692	<0.001
PMR	15.96	0.508	0.722	0.604	0.050	0.524–0.684	<0.001
RDW	14.05	0.69	0.760	0.753	<0.001	0.691–0.815	0.012
CRP (N=3668)	1.065	0.867	0.578	0.763	<0.001	0.699–0.826	0.064
ESR (mm/L) (N=3966)	12.5	0.771	0.563	0.673	<0.001	0.590–0.756	0.002
Combined indicators							
NLR+LMR	15.963	0.938	0.623	0.849	<0.001	0.810–0.888	0.808
NLR+ENR	0.018	0.766	0.740	0.818	<0.001	0.768–0.869	0.063
NLR+PLR	0.011	0.875	0.673	0.839	<0.001	0.791–0.886	0.548
NLR+ELR	0.012	0.859	0.688	0.836	<0.001	0.824–0.847	0.280
Multiple indicators							
NLR+PLR+LMR	0.011	0.891	0.698	0.860	<0.001	0.821–0.898	0.167
NLR+LMR+ENR	0.020	0.719	0.809	0.829	<0.001	0.780–0.878	0.249
NLR+ELR+LMR	0.011	0.922	0.634	0.845	<0.001	0.834–0.856	0.887
NLR+ENR+PLR	0.019	0.734	0.775	0.822	<0.001	0.771–0.874	0.157
NLR+ENR+ELR	0.019	0.766	0.731	0.825	<0.001	0.813–0.836	0.105
NLR+ELR+PLR	0.012	0.813	0.734	0.833	<0.001	0.821–0.844	0.361
NLR+LMR+ENR+PLR	0.018	0.781	0.771	0.835	<0.001	0.786–0.885	0.477
NLR+LMR+PLR+ELR	0.011	0.922	0.678	0.857	<0.001	0.846–0.867	0.407
NLR+LMR+ENR+ELR	0.021	0.719	0.805	0.834	<0.001	0.822–0.845	0.346
NLR+ENR+PLR+ELR	0.017	0.812	0.717	0.827	<0.001	0.815–0.838	0.257
NLR+LMR+ENR+PLR+ELR	0.017	0.797	0.727	0.837	<0.001	0.826–0.848	0.548

Notes: ^aZ-P value was calculated by MedCalc software. The value of Z-P means the difference between NLR and other inflammatory biomarkers.

Abbreviations: NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; ENR, eosinophil to neutrophil ratio; PLR, platelet to lymphocyte ratio; RDW, red cell volume distribution width; ELR, eosinophil to lymphocyte ratio; PMR, platelet to mean platelet volume ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AUC, area under concentration time curve; CI, confidence interval; NE, No evaluation.

were less than 0.7 (Figure 2). Although the Z-P value between NLR and CRP was 0.064, it was shown that NLR as a new inflammatory biomarker was not inferior to traditional biomarker, and it was even better than ESR, which was one of the traditional biomarkers (Z-P = 0.002). The cut-off values for predicting in-hospital mortality were $NLR \geq 4.43$, $LMR \geq 0.38$, $ENR \leq 0.01$ and $PLR \geq 176.49$. Next, we investigated the predictive value of different biomarker combinations. The results showed that NLR + PLR + LMR increased the predictive sensitivity, with

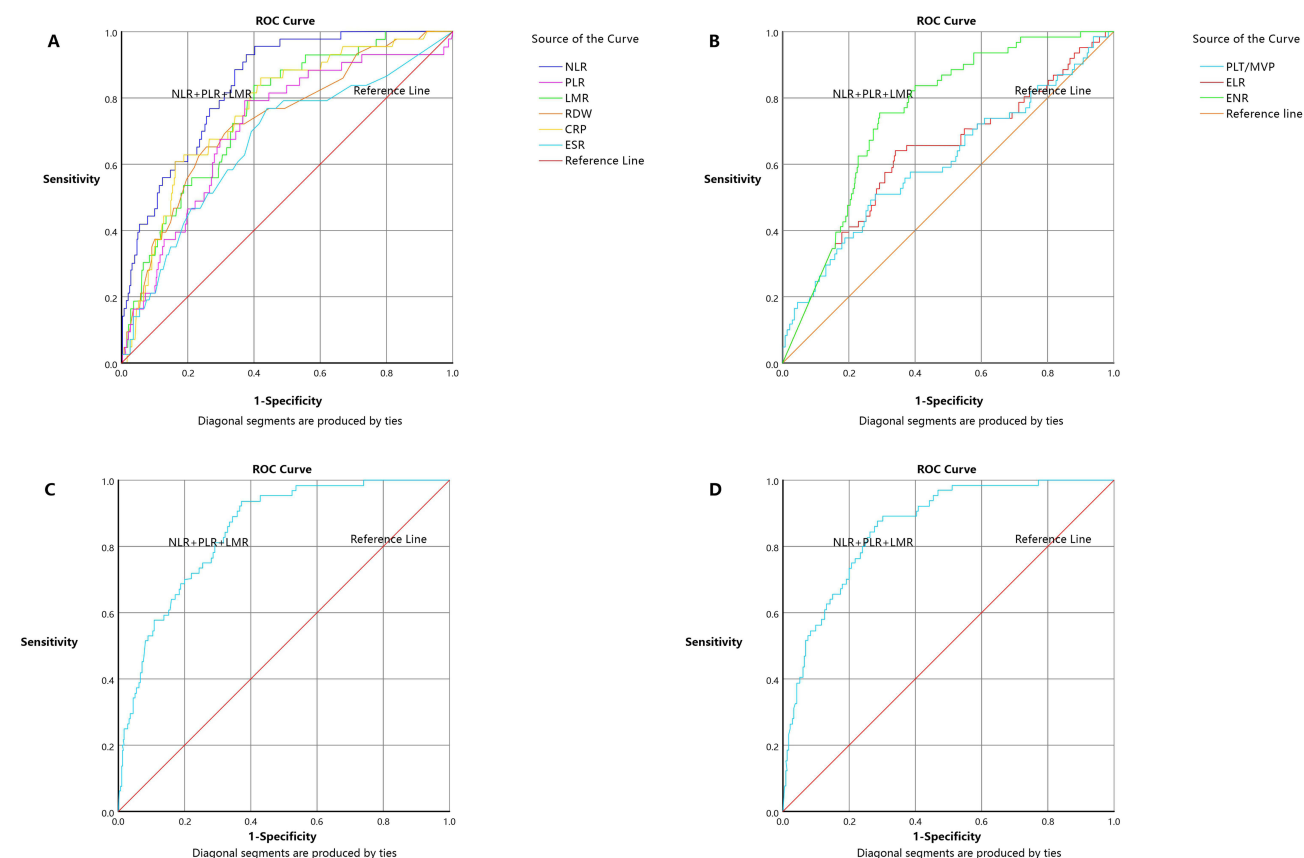


Figure 2 Curves of the novel inflammatory biomarkers.

Notes: (A): Inflammatory biomarkers positively associated with in-hospital mortality; (B): Inflammatory biomarkers negatively associated with in-hospital mortality; (C): ROC curve of NLR+LMR; (D): ROC curve of NLR+PLR+LMR;

a maximum AUC of 0.860 (95% CI 0.821–0.898; $P < 0.001$), sensitivity of 89.1%, and specificity of 69.8%. However, compared with NLR, the predictive power of NLR + PLR + LMR was not superior to it ($Z\text{-}P = 0.167$). Similarly, regardless of whether combined biomarkers or multiple biomarkers were used, the predictive effect of the NLR was not inferior to them (with $Z\text{-}P > 0.05$). As a result, the application of the NLR alone rather than combined with other novel inflammatory biomarkers can be considered in clinical work to predict the clinical outcomes of patients.

According to multivariate logistic regression analysis, $\text{NLR} \geq 4.43$ (OR, 3.308; 95% CI, 1.235–8.856; $P = 0.017$), $\text{LMR} \geq 0.38$ (OR, 2.343; 95% CI, 1.080–5.080; $P = 0.031$), $\text{ELR} \leq 0.01$ (OR, 2.343; 95% CI, 1.198–4.577; $P = 0.013$), age (OR, 1.066; 95% CI, 1.028–1.107; $P = 0.001$), comorbidities ≥ 2 (OR, 3.916; 95% CI, 1.752–8.751; $P = 0.001$), blood glucose (OR, 1.095; 95% CI, 1.028–1.166; $P = 0.005$), albumin (OR, 0.876; 95% CI, 0.834–0.919; $P < 0.001$) and RDW (OR, 1.317; 95% CI, 1.176–1.475; $P < 0.001$) were independent risk factors for in-hospital mortality (Table 4). We also tried to include erythrocyte count, hemoglobin, MPV, serum creatinine, SGOT, protein and LDL, but they were excluded from the equation ($p > 0.05$).

Patient Outcomes Grouped by the NLR Cut-off Value

Table 5 shows the baseline characteristics, laboratory tests, treatments and clinical outcomes of the patients grouped by the NLR cut-off value. Three patients without NLR data were excluded. Compared to patients with $\text{NLR} < 4.43$, patients in the group with $\text{NLR} \geq 4.43$ were older (74.00 [66.00–80.00] vs 69.00 [62.00–77.00], $P < 0.001$) and had more males (1137 [76.8%] vs 1999 [72.6%], $P = 0.003$) and comorbidities (2.00 [1.00–3.00] vs 2.00 [0.00–3.00], $P < 0.001$). In terms

Table 4 Logistic Regression Analysis of Risk Factors for Hospital Mortality

	OR	95% CI		P-value
		Lower	Upper	
Age	1.066	1.028	1.107	0.001
≥ 2 Comorbidities	3.916	1.752	8.751	0.001
Blood glucose	1.095	1.028	1.166	0.005
Albumin	0.876	0.834	0.919	<0.001
NLR ≥ 4.43	3.308	1.235	8.856	0.017
LMR ≥ 0.38	2.343	1.080	5.080	0.031
ELR ≤ 0.01	2.342	1.198	4.577	0.013
RDW	1.317	1.176	1.475	<0.001

Abbreviations: NLR neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; ELR, eosinophil to lymphocyte ratio; RDW, red cell volume distribution width; OR, odds ratios; CI, confidence interval.

Table 5 Patient Data Grouped Based on NLR Cut-off Value

	Overall (n=4232)	NLR<4.43 (n=2752)	NLR≥4.43 (n=1480)	P-value
Demographics				
Male (n, %)	3136(74.1%)	1999(72.6%)	1137(76.8%)	0.003
Age, year (median, 25th–75th percentiles)	71.00(63.00–78.00)	69.00(62.00–77.00)	74.00(66.00–80.00)	<0.001
BMI, kg/m ² (median, 25th–75th percentiles) (n=1513)	22.96(20.07–26.02)	23.18(20.28–26.15)	22.32(19.53–25.71)	0.002
Smoking status (n, %)(n=4122)				
Ever smoker	3035(73.6%)	1951(72.6%)	1084(75.5%)	0.048
Current smoker	976(23.7%)	667(24.8%)	309(21.5%)	0.017
Former smoker	2059(50.0%)	1284(47.8%)	775(54.0%)	<0.001
Never smoker	1087(26.4%)	735(27.4%)	352(24.5%)	0.048
Pack year (median, 25th–75th percentiles)(n=2864)	365.00(273.75–547.50)	365.00(273.75–547.50)	365.00(273.75–547.50)	0.357
Symptom (n, %)				
Chest distress	351(8.3%)	251(9.1%)	100(6.8%)	0.008
Breathe hard	822(19.4%)	589(21.4%)	233(15.7%)	<0.001
Cough	3353(79.2%)	2156(78.3%)	1197(80.9%)	0.530
Expectoration	2910(68.8%)	1848(67.2%)	1062(71.8%)	0.002
Comorbidities (n, %)				
Diabetes mellitus	680(16.1%)	422(15.3%)	258(17.4%)	0.076
Chronic renal failure	216(5.1%)	96(3.5%)	120(8.1%)	<0.001
Heart failure	136(3.2%)	55(2.0%)	81(5.5%)	<0.001

(Continued)

Table 5 (Continued).

	Overall (n=4232)	NLR<4.43 (n=2752)	NLR≥4.43 (n=1480)	P-value
Cardiovascular disease	2903(68.6%)	1772(64.4%)	1131(76.4%)	<0.001
Arrhythmia	457(10.8%)	243(8.8%)	214(14.5%)	<0.001
Hypertension	1882(44.5%)	1170(42.5%)	712(48.1%)	<0.001
Cerebrovascular disease	529(12.5%)	343(12.5%)	186(12.6%)	0.922
Malignancy	209(4.9%)	104(3.8%)	105(7.1%)	<0.001
Anxiety/depression	110(2.6%)	65(2.4%)	45(3.0%)	0.186
Osteoporosis	126(3.0%)	87(3.2%)	39(2.6%)	0.337
≥2 comorbidities	2362(55.8%)	1428(51.9%)	934(63.1%)	<0.001
None	1870(44.2%)	1324(48.1%)	546(36.9%)	<0.001
Total number of comorbidities (median, 25th–75th percentiles)	2.00(1.00–3.00)	2.00(0.00–3.00)	2.00(1.00–3.00)	<0.001
Arterial blood gases (median, 25th–75th percentiles)				
pH (N=1015)	7.40(7.37–7.42)	7.40(7.37–7.42)	7.40(7.36–7.42)	0.890
PaCO ₂ (mmHg) (N=990)	39.15(34.00–48.40)	38.40(33.90–45.60)	40.90(34.30–53.70)	0.001
PaO ₂ (mmHg) (N=990)	79.50(69.80–91.45)	79.60(70.20–90.48)	79.20(68.40–93.03)	0.862
HCO ₃ ⁻ (mmol/L) (N=989)	24.70(21.80–28.70)	24.00(21.60–21.28)	25.85(22.20–31.20)	<0.001
PaO ₂ /FiO ₂ (mmHg) (N=881)	377.95(332.70–436.55)	377.60(334.63–431.75)	378.45(329.50–446.50)	0.635
Respiratory Index (N=784)	0.30(0.10–0.40)	0.30(0.20–0.40)	0.25(0.10–0.40)	0.589
Oxygen saturation (%) (N=990)	95.60(93.10–97.20)	95.70(93.60–97.20)	95.50(92.30–97.28)	0.260
Biochemistry values (median, 25th–75th percentiles)				
Blood glucose (mg/dL) (N=3904)	4.84(4.27–6.00)	4.67(4.20–5.40)	6.35(4.98–8.26)	<0.001
BUN (mg/dL) (N=1942)	5.81(4.67–7.24)	5.63(4.57–6.82)	6.35(4.98–8.26)	<0.001
Serum creatinine (mg/dL) (N=4119)	68.90(57.80–82.10)	68.10(58.10–79.98)	70.50(57.30–88.00)	<0.001
Sodium (mmol/L) (N=4156)	140.40(137.70–142.50)	140.70(138.60–142.70)	139.40(136.20–142.10)	<0.001
Potassium (mmol/L) (N=4155)	4.00(3.70–4.30)	3.90(3.60–4.20)	4.00(3.70–4.40)	<0.001
SGOT (U/L) (N=4071)	20.00(17.00–26.00)	20.00(17.00–25.00)	21.00(17.00–29.00)	<0.001
SGPT (U/L) (N=4074)	17.00(12.00–23.00)	16.00(12.00–23.00)	17.00(13.00–25.00)	<0.001
Protein (g/dL) (N=2170)	63.40(59.40–67.50)	64.00(60.30–67.70)	62.10(57.40–67.00)	<0.001
Albumin (g/dL) (N=4012)	35.80(32.30–38.80)	36.6(33.70–39.20)	33.80(29.6–37.30)	<0.001
LDL (mmol/L) (N=3894)	2.30(1.80–2.88)	2.40(1.90–2.91)	2.19(1.68–2.70)	<0.001
NT-proBNP (ng/L)(N=3102)	180.60(69.28–644.70)	118.700(53.43–339.58)	457.20(159.20–1290.5)	<0.001
D-Dimer (mg/L) (N=1454)	0.52(0.27–1.11)	0.50(0.26–1.03)	0.59(0.30–1.37)	<0.001
D-Dimer abnormal (n, %)	758(52.2%)	490(64.6%)	268(35.4%)	0.010

(Continued)

Table 5 (Continued).

	Overall (n=4232)	NLR<4.43 (n=2752)	NLR≥4.43 (n=1480)	P-value
Treatment (n, %)				
Bronchodilator	3706(87.6%)	2371(86.2%)	1335(90.2%)	<0.001
Corticosteroid nebulization	2807(66.3%)	1777(64.4%)	1030(69.6%)	0.001
Systemic corticosteroid therapy	902(21.3%)	444(16.1%)	458(30.9%)	<0.001
Antimicrobial therapy	3684 (87.1%)	2274 (82.6%)	1410 (95.3%)	<0.001
Antifungal agents	433(17.5%)	174(6.3%)	259(17.5%)	<0.001
Expectorant	3688(87.1%)	2337(84.9%)	1351(91.3%)	<0.001
Respiratory support				
NIMV	354(8.4%)	168(6.1%)	186(12.6%)	<0.001
IMV	40(0.9%)	6(0.2%)	34(2.3%)	<0.001
NIMV+IMV	51(1.2%)	9(0.3%)	42(2.8%)	<0.001
Clinical outcome and the prognosis (n, %)				
Respiratory failure	1214(28.8%)	610(22.3%)	604(40.9%)	<0.001
Organ failure	2240(52.9%)	1301(47.3%)	939(63.4%)	<0.001
LOS, days (median, 25th–75th percentiles)	10.00(8.00–14.00)	10.00(8.00–13.00)	12.00(9.00–15.00)	<0.001
LOS>14 days	864(20.4%)	421(15.3%)	443(29.9%)	<0.001
Admitted to ICU	168(4.0%)	32(1.2%)	136(9.2%)	<0.001
Treatment failure	1480(35%)	381(23.6%)	1099(42.0%)	<0.001
Hospitalization expenses (median, 25th–75th percentiles)(N=4210)	13,702.25(10,006.37–19,545.10)	12,397.97(9310.04–16,622.39)	17,215.64(12,105.60–26,498.85)	<0.001
First readmissions due to AECOPD (N=1307)				
Within 1 month after discharge	166(12.7%)	80(10.2%)	86(16.4%)	0.001
Within 2 months after discharge	257(19.7%)	125(15.9%)	132(25.2%)	<0.001
Within 3 months after discharge	337(25.8%)	179(22.8%)	158(30.2%)	0.003
Within 12 months after discharge	839(64.2%)	477(60.8%)	362(69.2%)	0.002
Within 15 months after discharge	942(72.1%)	549(70.0%)	393(75.1%)	0.043
Within 24 months after discharge	1150(88.0%)	679(86.6%)	471(90.1%)	0.060
Long-term mortality				
One-year mortality after the index hospitalization	56(1.3%)	22(0.8%)	34(2.3%)	<0.001
Overall mortality ^a	437(10.3%)	215(7.8%)	222(15.0%)	<0.001

Notes: ^aThe data were analyzed according to the death of the last hospitalization in the Hospital electronic medical record database (EMRD) of Chaoyang Hospital.

Abbreviations: BMI, body mass index; pH, potential of hydrogen; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; HCO₃⁻, bicarbonate; FiO₂, fraction of inspired oxygen; BUN, blood urea nitrogen; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NLR, neutrophil to lymphocyte ratio; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation; LOS, length of stay in hospital; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit.

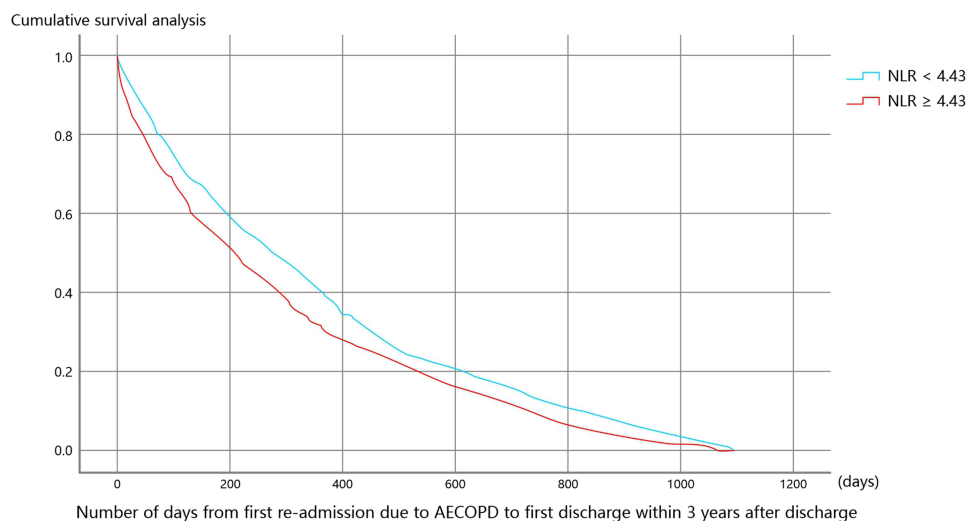


Figure 3 K–M curve of first readmissions due to AECOPD within 3 years after discharge.

of clinical outcomes, the $\text{NLR} \geq 4.43$ group had a longer LOS (12.00 [9.00–15.00] vs 10.00 [8.00–13.00], $P < 0.001$), higher rate of ICU admission (136 [9.2%] vs 32 [1.2%], $P < 0.001$), higher IMV application (34 [2.3%] vs 6 [0.2%], $P < 0.001$) and higher rate of treatment failure (1099 [42.0%] vs 381 [23.6%], $P < 0.001$) versus $\text{NLR} < 4.43$ group. In addition, patients with $\text{NLR} \geq 4.43$ had more hospitalization expenses (17,215.64 [12,105.60–26,498.85] vs 12,397.97 [9310.04–16,622.39], $P < 0.001$), and more patients were readmitted earlier due to AECOPD within 1 month, 2 months, 3 months, 12 months and 15 months after discharge than patients with $\text{NLR} < 4.43$. Based on the last recording at Chao-Yang Hospital, 537 patients died in the hospital and the median time between the first index hospitalization and the last hospitalization was 2 years (IQR 1.0 year–3.0 years). Higher one-year mortality after the index hospitalization (34 [2.3%] vs 22 [0.8%], $P < 0.001$) and overall mortality (222 [15.0%] vs 215 [7.8%], $P < 0.001$) were found among patients with $\text{NLR} \geq 4.43$ versus patients with $\text{NLR} < 4.43$ (Table 5). Based on the K–M curve, the patients with an $\text{NLR} \geq 4.43$ had a higher first readmission rate due to AECOPD after discharge than patients with $\text{NLR} < 4.43$ (Figure 3). The pooled data revealed that patients in the higher NLR group had a higher rate of all kinds of therapies included in this study (bronchodilator, corticosteroid nebulization, chemotherapeutic corticosteroid therapy, antimicrobial, antifungal agents, expectorant and respiratory support). All the differences reached statistical significance and are listed in Table 5. Through visual analysis of the first readmission data of all eligible patients due to AECOPD after discharge (2925 patients without related data were excluded from this analysis), the number of patients readmitted within one month after discharge due to AECOPD was the highest, reaching 166 (12.7%) (Figure 4).

Nomogram and Calibration Curve

Based on logistic regression analysis, the combination of age, ≥ 2 comorbidities, blood glucose, RDW, albumin, $\text{NLR} \geq 4.43$, $\text{LMR} \geq 0.38$ or $\text{ELR} \leq 0.01$ was considered an independent risk indicator to predict the risk of in-hospital mortality in AECOPD patients. Therefore, a nomogram was constructed to incorporate selected biomarkers (Figure 5). The calibration curve showed that the model was well calibrated. The AUC of the nomogram model and the C-index of the internal validation results were 0.914 (95% CI: 0.883 to 0.945) and 0.914, respectively (detailed results of the nomogram model validation are listed in Supplementary Figures 1, 2 and Supplementary Material 2).

Discussion

Main Findings in This Study

This study provided a number of novel inflammatory biomarkers that can predict the in-hospital mortality of AECOPD patients and verified their correlation with traditional biomarkers. The NLR, with the maximum AUC value, was

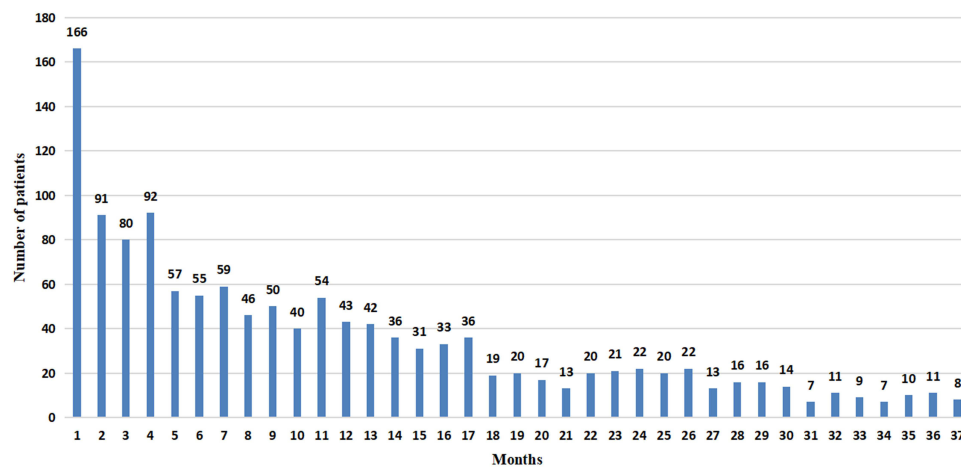


Figure 4 Number of initial readmissions due to AECOPD per month after discharge.

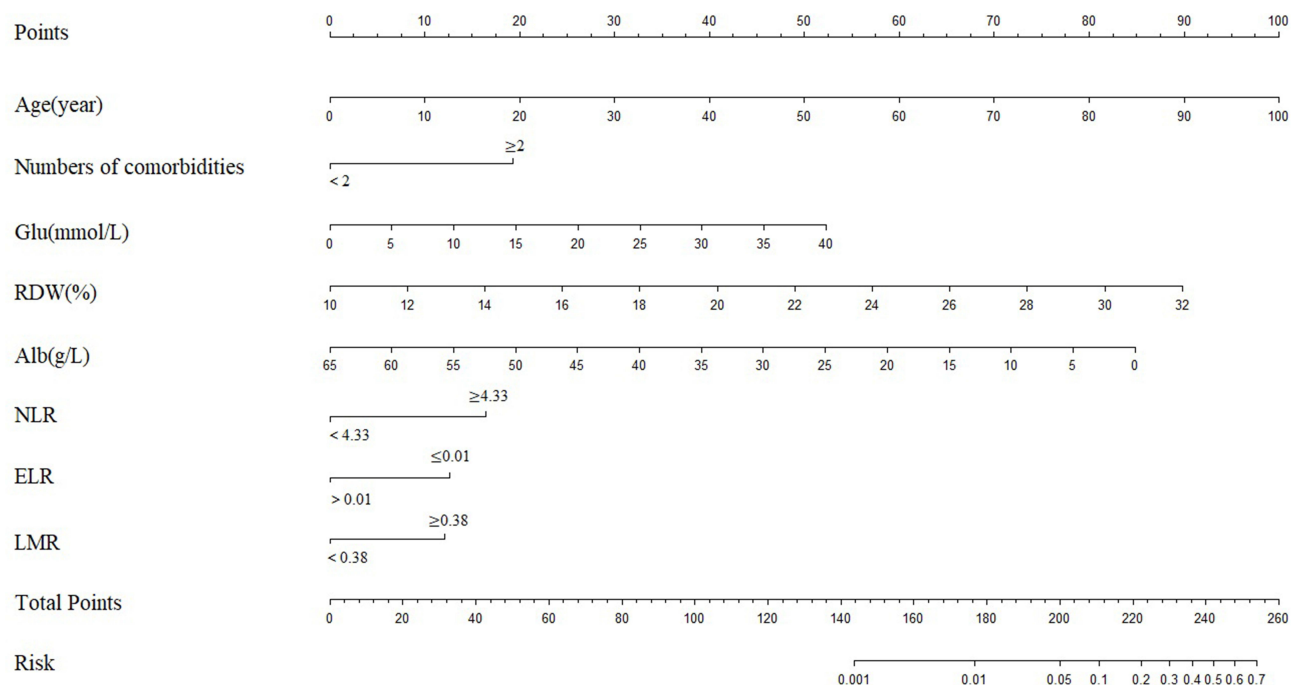


Figure 5 Nomogram for assessment of patient mortality risk.

Notes: To use a nomogram, draw a vertical line to identify the corresponding points of each variable according to its status. Then, sum the points of all variables to find the position on the total point axis. Draw a vertical line between the position and the lower line of the nomogram, you can determine patient mortality risk at the lower line of the nomogram.

considered to be the best single inflammatory biomarker compared with other novel inflammatory biomarkers in this study. In addition, the NLR was not inferior to CRP, a traditional biomarker, and combined inflammatory biomarkers and was even superior to traditional biomarkers such as ESR and RDW according to the results of the present study. This study revealed that the best cut-off value of NLR was 4.43, and patients with $\text{NLR} \geq 4.43$ were more likely to have more comorbidities (such as chronic renal failure, heart failure, cardiovascular disease and malignancy), higher treatment failure rate, organ failure rate, ICU admission, longer LOS and poorer long-term prognosis, such as one-year mortality after the index hospitalization and overall mortality, than patients with $\text{NLR} < 4.43$. Moreover, patients with a higher NLR (≥ 4.43) were more likely to be associated with higher and earlier AECOPD-related readmission within 15 months after discharge than patients with a lower NLR (< 4.43). The first readmission due to AECOPD was highest within one month

after discharge, suggesting that it is essential for physicians to improve the management and follow-up strength of AECOPD patients after discharge, especially during the early period.

Discussion of the Most Important Differences in the Present Study

To our knowledge, this is the largest retrospective study to date focused on the clinical predictive efficacy of novel inflammatory biomarkers among patients with AECOPD. The NLR is a cell inflammatory biomarker that can be easily derived from CBC tests. Previous studies revealed that the NLR was increased in several malignancies compared with patients with benign malignancies or healthy individuals.^{29–31} At the same time, the NLR was correlated with disease activity and clinical outcome in some chronic inflammatory diseases, such as hypertension, diabetes, and inflammatory bowel disease.³² Stable COPD patients with malignancies or metabolic syndrome, which might cause patients to be at risk of AECOPD, had higher NLR values than patients without these comorbidities.^{32,33} Most previous related studies focused on short-term outcomes, such as 28-day mortality,^{24,34} 90-day mortality,^{21,35} in-hospital mortality,^{36,37} LOS,^{34,38} ICU admission rate,^{34,38} etc. A recent meta-analysis demonstrated that the NLR of AECOPD patients was significantly associated with the risk of adverse outcomes (mortality, LOS, and ICU admission rate, need for IMV, pulmonary hypertension, etc., [OR = 1.054, 95% CI 1.016–1.093, P = 0.005]), which was consistent with our study.²⁵ However, the heterogeneity of the meta-analysis was significant, possibly because of the significant heterogeneity of the AECOPD patients contained in each study and the small sample size, which might cause higher sampling error.²⁵ Yao et al enrolled 146 AECOPD patients with heart failure, and pooled results showed that non-survival patients had significantly higher levels of NLR than survival patients, and the cut-off value of NLR was 16.83, although NLR did not have the maximum value of AUC compared with CRP/albumin.²⁴ While another study recruited 80 AECOPD patients and demonstrated that the cut-off value of NLR was 3.4, NLR was not the best biomarker to predict the diagnosis of AECOPD patients compared with pressure of carbon dioxide (PaCO₂).³⁹ Yao et al reported that the combination of NLR, PLR, and CRP could increase the sensitivity of prognosis compared with NLR.⁵ Although the NLR combined with the LMR and PLR had the largest AUC value in this study, the predictive effect of the NLR was inferior to that of the NLR combined with the LMR and PLR, thus the combination of multiple inflammatory biomarkers would inevitably increase the burden on physicians.

Several studies have focused on short-term outcomes, and relatively little is known regarding the prognostic ability of the NLR for long-term outcomes, such as the risk of readmission after discharge, one-year mortality after the index hospitalization and overall mortality. In this study, patients with NLR ≥ 4.43 were more likely readmitted due to AECOPD within 1 month, 2 months, 3 months, 12 months and 15 months after discharge than patients with NLR < 4.43 . However, this difference did not exist in the relevant data within 24 months after discharge. Another study in Turkey found that outpatients with an NLR greater than 4.50 with a non-eosinophilic exacerbation on admission had an increased risk of readmission in the first month, which was similar to the findings of this study.⁴⁰ However, a study published in 2022 enrolled 170 AECOPD patients and revealed that patients in the readmission group (>1 readmission) had a lower NLR than patients in the non-readmission group (≤ 1 readmission) (7.17 ± 8.95 vs 14.42 ± 31.17 , P = 0.001), which was contrary to our study.⁴¹ This may be because the patients in the non-readmission group had a higher proportion of systematic corticosteroid application, which might increase the number of neutrophils and cause lymphocytes to be killed and dissolved, leading to an increase in NLR.⁴¹ At the same time, the different definitions of readmission groups might cause the different outcomes.⁴¹ In addition to the NLR, peripheral blood eosinophil levels were used to evaluate the long-term outcomes among AECOPD patients. A previous study revealed that AE of COPD during 1 year was greater among COPD patients with blood eosinophil counts higher than or equal to 300 cells/mm³ (rate ratio [RR] 1.25; 95% CI 1.10–1.43), higher than or equal to 400 cells/mm³ (RR 1.48; 95% CI 1.26–1.75), and higher than or equal to 500 cells/mm³ (RR 1.76; 95% CI 1.45–2.14), respectively, versus patients with blood eosinophil counts less than those cut-offs.⁴² Another study contained 811 AECOPD patients and reported that patients in the eosinophilic group (blood eosinophil counts $\geq 0.30 \times 10^9$ cells/L) had lower 3-year mortality than patients in the non-eosinophilic group (blood eosinophil counts $< 0.30 \times 10^9$ cells/L) (40% vs 54%, P = 0.006).⁴³ Although eosinophil was not assessed in this study, the novel inflammatory biomarkers such as ENR and ELR were inversely associated with in-

hospital mortality. Moreover, this study showed that NLR could also predict long-term clinical prognosis, which provided an alternative clinical assessment method among AECOPD patients.

Besides, the pooled results of this study showed that nearly one-quarter of patients were readmitted for AECOPD for the first time within 3 months, and this proportion reached two-thirds within 1 year. In addition, the first readmission due to AECOPD in patients was more likely to occur within 1 month after discharge than in any subsequent month, reaching 12.7%. A study in China showed that the readmission rate of patients with COPD presenting with acute exacerbation within 30 days was 21.52%.⁴⁴ A systematic review and meta-analysis published in 2020 including 57 studies indicated that the prevalence of COPD-related readmission varied from 2.6 to 82.2% at 30 days and 25.0–87.0% at 12 months post-discharge.⁴⁵ The significant heterogeneity of the readmission rate may reflect variations in study methodology and the local context, such as ethnicity, disease diagnosis method, and health care quality. However, overall, the relatively high readmission rates and a large proportion of early readmissions in COPD patients after discharge were undoubted, which indicated the need for improving the quality of treatment and health care during hospitalization and post-discharge. Improving access to primary health care and providing care bundles (including consults, inpatient interventions, education, transitions of care, and after discharge care) are effective strategies to decrease hospital readmissions.⁴⁶ Furthermore, the impact of COVID-19 among AECOPD patients should be interpreted. According to a meta analysis including 13 studies assessing the influence of COVID-19 on readmission rates among AECOPD patients, age is the most dominant risk factor for readmission rate, followed by diabetes, high LOS, COPD, chronic kidney disease, liver disease, metastatic disease and coronary artery disease, and COVID-19 was not superior to them.⁴⁷ Donnelly et al compared the readmission rate between survival patients with COVID-19, pneumonia, or heart failure. And the pooled results revealed that COVID-19 survivors had lower rates of 60-day readmission and death than patients with pneumonia (26.1 vs 31.7%; $p = 0.006$), or heart failure (27.0% vs 37.0%; $p < 0.001$).⁴⁸ As a result, management of chronic diseases and comorbidities remains the key to preventing readmission among patients with COPD.

Strengths and Limitations

To the best of our knowledge, this study was the most comprehensive study covering novel inflammatory biomarkers and had the largest sample size thus far. In addition to exploring the predictive ability of single indicators, the predictive ability of the combinations of multiple inflammatory biomarkers for clinical outcomes was also analyzed in this study. At the same time, this study used a more scientific method to compare the different AUCs between traditional and novel inflammatory biomarkers to find the predictors with real statistical differences. In addition, a nomogram was established to visualize the pooled results and offer help to clinicians for a more intuitive assessment of mortality risk among AECOPD patients. Furthermore, treatment failure (a composite index), time of first readmission after discharge, one-year mortality after the index hospitalization and overall mortality were first assessed, which further proved the predictive value of the NLR for the treatment effect of AECOPD patients during hospitalization and after discharge. This study still has several limitations. First, it was a single-center retrospective observational study, and the biases inherent in this type of study should not be ignored. Second, some relevant data, such as stable COPD severity and spirometry data of all patients and microbiological data, were not recorded in the EMRD. Then, the generalization of our nomogram should be interpreted with caution due to the absence of external validation. Considering the possibilities of error coding of ICD among patients, prospective studies and experienced respiratory physicians will be needed to recruit eligible patients.

Unanswered Questions and Future Research

Because of the limitations mentioned above, more high-quality prospective studies with large sample sizes are warranted in the future to further investigate the predictive ability of the NLR and the clinical feasibility of the nomogram in this study. At the same time, further studies should pay more attention to biomarkers that can predict long-term outcomes, such as the readmission rate and long-term mortality, among AECOPD patients and establish the potential clinical use of the NLR alone or in combination with other inflammatory biomarkers. Finally, the stability and test time of the NLR in AECOPD patients should also be noted and analyzed in the future.

Conclusion

The NLR was the best single inflammatory biomarker to predict in-hospital and long-term mortality, treatment failure, organ failure and the first readmission due to AECOPD (within 15 months) among AECOPD patients. The appropriate cut-off value of NLR was 4.43. AECOPD should be monitored carefully, especially within the first month after discharge, which requires better quality, personalized and convenient follow-up methods to be proposed for patients with AECOPD post-discharge.

Abbreviations

AECOPD, Acute exacerbation of chronic obstructive pulmonary disease; NLR, Neutrophil–lymphocyte ratio; PLR, Platelet–lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; ENR, Eosinophil-to-neutrophil ratio; ELR, Eosinophil-to-lymphocyte ratio; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PMR, Platelet to mean platelet volume ratio; ROC, Receiver-operating characteristic; KM, Kaplan–Meier; WHO, World Health Organization; PCT, Procalcitonin; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; NIPPV, Non-invasive positive pressure ventilation; CAP, Community acquired pneumonia; CBC, Complete blood count; EMRD, Electronic medical record database; NIMV Non-invasive mechanical ventilation; IMV, Invasive mechanical ventilation; LOS, Length of stay; ICU, Intensive care unit; IQR, Interquartile range; ROC, Receiver-operating characteristic; OR, Odds ratios; CIs, Confidence intervals; K–M, Kaplan–Meier; BMI, Body mass index; RDW, Red blood cell distribution width; MPV, Mean platelet volume; BUN, Blood urea nitrogen; SGOT, Serum glutamic-oxaloacetic transaminase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL, Low-density lipoprotein; SGPT, Serum glutamic pyruvic transaminase; MCV, Mean corpuscular volume; PLT, Platelet; PaCO₂, Pressure of carbon dioxide; HCO₃, Bicarbonate; ALB, Albumin; RR, Rate ratio; GOLD, Global initiative for chronic obstructive lung disease; AUC, Area under curve; COVID-19, Corona Virus Disease 2019; C-index, Concordance index.

Data Sharing Statement

Data about individual deidentified participants of this trial will be available from the corresponding author Zhaohui Tong (Email: tongzhaohuicy@sina.com) on reasonable request after the main results of the study have been published.

Ethics Statement

This study was approved by the Research Ethics Board of Beijing Chao-Yang Hospital (project approval number: 2020-ke-544). This study complies with the declaration of Helsinki.

Informed Consent Statement

Informed consent was waived due to the anonymous and mandatory nature of the data.

Author Contributions

Shuai Shao developed the initial idea of this study. Shuai Shao, Zhijing Zhang made their contributions to study design, execution, acquisition of data, analysis, interpretation and writing of this article. Zhaohui Tong, Lin Feng and Lirong Liang also made significantly contributed to this work in study execution, acquisition of data, interpretation of this article. Lirong Liang and Lin Feng critically reviewed the article. Zhaohui Tong substantially revised this article and provided revision suggestions for it to make it better. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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